REMARKS/ARGUMENTS

Claims 1-13 are pending in the present application. These claims are all rejected under 35 U.S.C. 103 as indicated below. Reconsideration of the application is respectfully requested.

Rejection Under 35 U.S.C. §103

Claims 1-13 are rejected at p. 2 of the present Office Action under 35 U.S.C. 103 over the combined teaching of Lidor-Hadas et al. (USP 7,038,083), Gall et al. (USP 4,927,814), Blum et al. (USP 4,407,761), Blum et al. (DE 2702631) and Kruger et al. (DE 2658961) in view of Hancock et al., Journal of Pharmaceutical Sciences, Jan. 1997, Vol. 86, No. 1, pp. 1-12, for the reasons set forth at pp, 2-3 of the Action. The rejection is respectfully traversed.

The main drawback underlying the syntheses of diphosphonic acids is the formation of solid, or semi-solid reaction masses during the phosphorylation step. This problem, which is discussed in J. Org. Chem. (1995) 60, pp. 8310-8312 (cited at p. 2, line 25 of applicants' specification) renders it impossible to carry out the process on an industrial scale in a manner which assures the safety of those carrying out the reaction. This is due to the fact that, as applicants can attest, the formation of solid or semi-solid reaction masses during the reaction in question does not allow stirring of the reaction vessel. Consequently, one is not able to maintain an effective control of the reaction temperature. The resulting high temperatures that are encountered, therefore, lead to the sublimation of white and/or yellow phosphorous which, in turn, reacts violently upon coming into contact with air. As, thus, one of ordinary skill in this field would immediately recognize, the industrialization of the subject process, when practiced in its "known", i.e., prior art form, is simply not feasible.

The process disclosed in the primary reference cited to reject the applicants' claims, i.e., USP 7,038,083 to Lidor-Hadas, is subject to exactly the deficiency as noted above, , i.e., the formation of a solid or semi-solid reaction mass which inhibits or entirely prevents stirring of the reaction vessel and which, thus, does not permit the control of the temperature within the vessel, leading to the sublimation/explosion problems described above. For this reason the process as described in the subject reference is incapable of being 'ramped up' to an industrial scale.

Evidence of the above-described deficiency is provided, *inter alia*, by the disclosure

contained in, e.g., examples 1, 6, 7, 11 and 12 of the subject reference, each of which mentions the formation of reaction masses of the type discussed above. The formation of these solid phases is not surprising to those having an ordinary level of skill in this art since it is well-known among such individuals that aromatic hydrocarbons do not form a homogeneous phase with the reaction mass of the phosphorylation reaction. Furthermore, the aromatic hydrocarbons and silicon-based fluids which also constitute some of the products formed by the reaction described by the subject reference serve to contaminate the active material which is the reason for carrying out the reaction in the first place.

For the reasons presented above, therefore, one having at least an ordinary level of skill in the relevant field would not start with the method as described in Lidor-Hadas in searching for an improved method for forming the diphosphonic acids according to applicants' claims. Furthermore, for the reasons presented below in the discussing concerning the secondary references combined by the Examiner with Lidor-Hadas, even the combination of one or more of said secondary references with Lidor-Hadas would not remedy the known deficiencies attributable to the method as taught by the primary reference (see the discussion above) and thus the combination of Lidor-Hadas with said secondary references, individually or collectively, in whole or in part, would in no way achieve the method as recited in the presently pending claims of this application.

More particularly, Example 2 in U.S. Patent No. 4,407,761 of Blum et al. expressly states that the reaction results in a reaction product that can no longer be stirred. Therefore, this process could never be used in a manufacturing line since doing so would mean that no control of the temperature was possible, thus permitting sublimation of white and/or yellow phosphorous, resulting in a violent (and thus dangerous) reaction upon contact of this material with any of the surrounding air.

Further to the above, Blum et al. DE 2702631 also discloses that the reaction mass becomes "viscous". Thus the reaction would inherently suffer from the same deficiencies as discussed above with regard to several of the other prior art references included by the Examiner in the cited combination relied upon to reject applicants' claims.

Still further, the Kruger et al. DE 2658961 reference is primarily concerned with exothermic reactions which involve significant increases in the temperature of the reactants as the reaction(s) takes place. The temperature increases are to such an extent as to render the subject reactions

impractical for use in an industrial process.

Contrary, moreover to the references discussed above, the process as described and claimed in the present application, wherein a well-defined ratio of carboxylic acid, phosphorous oxychloride and phosphorous acid are used, permits the technician to maintain a perfectly homogeneous reaction mass which may, therefor, be stirred throughout the entire course of the reaction. This permits the efficient control of the reaction temperature and thus eliminates the risk of violent reactions which can endanger the safety of the worker(s) and any possible bystanders. The presently claimed process, therefore, may readily be scaled up to an industrial scale, thus permitting the effective (and relatively safe) production of the diphosphonic acids of general formula (I).

Further to the above, with regard to the Gall et al. USP 4,927,814 patent also included in the combination proposed by the Examiner, applicants submit that Example 7 of the subject patent describes the salification of a diphosphonic acid with a stoichiometric amount of 1N NaOH to form the crystalline disodium monohydrate salt of the compound. This document, thus, teaches away from obtaining the amorphous form(s) of the diphosphonic acids (however, see applicants' claim 5). Additionally, the combination of the '814 patent with the Hancock et al. J. of Pharmaceutical Sciences article would not in any manner teach or even suggest the preparation of a an amorphous monosodium salt of ibandronate (as recited, e.g., in claim 5).

Based upon the reasons presented herein, therefore, applicants respectfully submit that the present claims 1-13 of the application would not be obvious to one having an ordinary level of skill in this art over the teaching of the six references cited in combination to reject them. The Examiner is, thus, respectfully requested to reconsider and withdraw the claim rejections and to issue a Notice of Allowance for the entire application.

Respectfully submitted,

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